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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/993,333 | 11/14/2001 | Larry Wayne Oberley | 875.042US1 | 5690 |

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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402-0938

| EXAMINER | |
|---|---|
| SCHULTZ, JAMES | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/993,333 | OBERLEY ET AL. | |
| | Examiner | Art Unit | |
| | J. D. Schultz, Ph.D. | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,3,5-8,11-15 and 18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20, 21* is/are allowed.

6)☒ Claim(s) *2,3,5-8,11-15,18,19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed 24 March 2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 23 September 2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments, 35 U.S.C. § 112 first paragraph*

Claims 2, 3, 5-8, 11-15, 18, 19 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the Office action dated June 18, 2002.

There is apparent confusion in the interpretation of the instant claims, whereby Applicants appear to believe that the claims are limited only to those oligonucleotides that bind to one of the start codons of five recited antioxidant enzymes. This is not adopted.

A careful reading demonstrates that the claims do not require binding only to a start codon of the mRNA transcript encoding one of the five antioxidant enzymes, or even to any part of the mRNA transcript encoding one of the antioxidant enzymes in general, but rather to "a nucleic acid" that encodes a start codon from one of five antioxidant enzymes.

Independent claim 6 recites:

> "An oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding a human antioxidant enzyme start codon, wherein the antisense sequence is about 18 to 26 nucleotides in length, and wherein the antioxidant enzyme ..." is chosen from one of five different enzymes.

Since the start codons of these five enzymes are identical not only to each other, but also to the vast majority of all start codons, it is emphasized that the claims as written embrace more than just antisense to any of the five recited antioxidant enzymes. Rather, as worded, the claims read on an antisense oligo that targets any portion of any nucleic acid, so long as that nucleic acid encodes a human start codon that also happens to be found in any of the five recited human antioxidant enzymes.

Since the start codons of all five enzymes are not only identical to each other (see applicant's response of July 6, 2004 at page 9, 2nd paragraph), but also to virtually every other known start codon in general, the limitation that the start codon must be from one of the five enzymes does not really further limit, since it is well known in the art that most all start codons of a given mRNA comprise an AUG nucleotide motif. This motif is very highly conserved across most every gene and species with very few exceptions (see attached photocopy from page 121 of Molecular Biology of the Cell, 3rd Ed., 1995, Darnell *et al.*, Scientific American Books, NY, New York, where it is stated that "The 'start' (initiator) codon AUG specifies the amino acid methionine: all protein chains in prokaryotic and eukaryotic cells begin with this amino acid"). Thus it is maintained that the claim language encompasses any antisense targeted to most any RNA target, across most any species, so long as the nucleotide sequence contains the highly ubiquitous AUG start codon motif.

Furthermore, it is noted that Applicants incorrectly restate the rejection's basis: "In particular, the Examiner asserts that the claims are directed towards 'any' portion of 'any' nucleic acid so long as the oligonucleotide binds to a start codon of one of the five recited human antioxidant enzymes." This is too narrow an interpretation of the rejection; Applicants claims are in reality much broader than this. The claims read on an antisense oligo that targets any portion of any nucleic acid, so long as that nucleic acid contains a human start codon that also happens to be found in any of the five recited human antioxidant enzymes, which, as pointed out above, is the same start codon found on virtually any mRNA. In applicants recitation, it is incorrectly suggested that the claimed oligos must bind to a start codon from one of the five antioxidant enzymes, whereas the rejection (indeed, the claim itself) states that it may bind to any transcript containing the highly ubiquitous AUG start codon.

Applicants point to page 3, line 27 through page 4, line 27 in arguing that the application in discloses examples of antisense oligonucleotides that support the breadth claimed, in particular suggesting that antisense oligonucleotides that specifically bind to a contiguous portion of nucleic acid that includes a start codon for MnSOD, (SEQ ID Nos: 1-3), antisense oligonucleotides that specifically bind to a contiguous portion of nucleic acid that includes a start codon for CAT (SEQ ID Nos: 4-5), and antisense oligonucleotides that specifically bind to a contiguous portion of nucleic acid that includes a start codon for phospholipid GPX (SEQ ID Nos: 6-7) provide support for the breadth of any antisense to any target containing the AUG nucleic acid motif. However, in response it is reiterated that the provision of 7 antisense oligos would not support the genus of any antisense directed against any transcript containing the AUG

motif, because such a genus includes all mRNA transcripts as well as all variants, fragments, homologs, or alleles from any species, known or yet to be discovered that contain said motif.

Although Applicants argue that at the time the present application was filed the art worker knew of nucleic acid sequences for the five antioxidant enzymes, such knowledge would not support the breadth of any antisense directed to any mRNA transcript as well as any variant, fragment, homolog, or allele from any species, known or yet to be discovered that contain said motif.

Furthermore, even if the claims were amended to claim only those antisense oligos that are directed to any of the five recited human antioxidant enzymes, this would not be considered sufficient to overcome the instant written description rejection. While applicants have provided the sequence of manganese superoxide dismutase in the form of SEQ ID NO: 11 in the specification, and have subsequently pointed to GenBank accession numbers X02317, M21304, and AF199441 as teaching the sequences for copper and zinc superoxide dismutase and cytosolic glutathione peroxidase, this submission is not considered to provide adequate support for claims drawn to the broad genus of any such human target, because the claims are not limited to these, and because one of skill could not be apprised as to what structures present in these sequences allow one of skill to distinguish between a nucleic acid encoding a human antioxidant enzyme versus one that codes for a non-human version, particularly since mere recitation of these targets by name also encompasses all related mRNA transcripts such as variants, fragments, homologs, or alleles that encode proteins that retain the claimed antioxidant activity.

Neither the teaching of SEQ ID NO: 11 of specification nor the submission of the accession numbers of the prior art referred to above are considered to provide sufficient

distinguishing identifying characteristics of the genus of human antioxidant targets, because no accompanying description points out what structure/function relationship exists that would allow one of skill to determine whether that a nucleic acid sequence is indeed human. Therefore, one of skill in the art could not envision the antisense targets that belong to the genus of human manganese superoxide dismutase, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase as claimed, beyond those sequences provided.

However, and significantly, the claims are not limited to oligos targeted to the five antioxidant enzymes as argued, but rather encompass any antisense to any nucleic acid that encodes AUG, which is the start codon found in the five enzymes. Accordingly, applicants are not considered to be in possession of the genus antisense oligos to said targets as now broadly claimed.

Claims 8, 11-15, and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vivo* antisense-mediated inhibition of human superoxide dismutase in the treatment of tumors, does not reasonably provide enablement for treatment of any tumor, for the same reasons of record as set forth in the Office action mailed June 18, 2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants have asserted that the cancellation of subject matter in claim 8 thereby limits the claim to methods of treating tumors using antisense directed to human mnSOD, and should

therefore be considered enabled. However, this is not considered convincing, because as indicated above, the claim is not limited to methods of using antisense oligos that target human mnSOD, but rather encompasses methods of inhibiting tumors using antisense to any mRNA that contains the start codon of human mnSOD, for the same reasons as indicated above in the rejection under 35 U.S.C. § 112 first paragraph written description. Therefore, because the claims are not considered enabled for this breadth, and because Applicants have provided no further arguments regarding this rejection, the rejection under 35 U.S.C. § 112 first paragraph enablement of the claims above is maintained.

***Response to Claim Rejections - 35 USC § 102***

Claims 2, 3, 5-7, and 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez-Zulueta *et al.* (of record), for the same reasons as set forth in the action mailed 23 September 2004.

Applicants argue that Gonzalez-Zulueta et al. teach an antisense oligonucleotide targeted to a rat manganese superoxide dismutase, while the instant claims are directed to a human manganese superoxide dismutase, and therefore it is asserted that there is nothing in Gonzalez-zulueta et al. that discloses the recited oligonucleotide.

This argument has been fully considered but is not convincing, because the claims, as written, embrace more than just antisense to any of the five recited human antioxidant enzymes. Rather, as worded, the claims read on any antisense oligo so long as it targets any portion of any nucleic acid that encodes a human start codon that is found in any of the five recited human antioxidant enzymes. Gonzalez-Zulueta et al. teach a phosphorothioated antisense compound

targeted to a nucleic acid that encodes a human antioxidant enzyme start codon. Although the target of Gonzalez-Zulueta encodes a rat manganese superoxide dismutase (i.e. not human), the start codon is identical to the human start codon sequence. The oligo of Gonzalez Zulueta is 19 nucleotides long, which is considered to be about 20 nucleotides. Furthermore, because each of copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase all contain AUG/ATG "human" start codons, and because Gonzalez-Zulueta *et al.* teaches an antisense that targets a nucleic acid (i.e. manganese superoxide dismutase) that encodes this human start codon, Gonzalez-Zulueta is considered to anticipate compound claims reciting antisense to nucleic acids encoding the antioxidant enzymes.

### *Allowable Subject Matter*

Claims 20 and 21 are allowed, because the art does not teach or fairly suggest the sequence of SEQ ID NO: 2.

### *Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD

JAMES SCHULTZ
PATENT EXAMINER